CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074750

Trade Name : ACYCLOVIR CAPSULES 200mg

Generic Name: Acyclovir Capsules 200mg

Sponsor : Lek Pharmaceutical and Chemical Co

Approval Date: April 22, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074750

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074750

APPROVAL LETTER

ANDA 74-750

APR 22 ..

LEK Pharmaceutical and Chemical Company d.d.
Attention: A. Gašperlin
333 Sylvan Avenue, 2nd Floor
Englewood Cliffs, NJ 07632

Dear Sir:

This is in reference to your abbreviated new drug application dated September 15, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules, 200 mg.

Reference is also made to your correspondence dated March 26, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Capsules, 200 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Capsules, 200 mg of Glaxo Wellcome, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gordon R. Johnston for/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

4-22-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074750

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-750

MAR 21 1997

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Attention: A. Gašperlin
333 Sylvan Avenue, 2nd Floor
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Dear Sir:

This is in reference to your abbreviated new drug application dated September 15, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules, 200 mg.

Reference is also made to your amendment dated February 16, April 17, April 22 and August 7, 1996, and February 19, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly your application is **tentatively approved.** This determination is contingent upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug products) and is, therefore, subject to change on the basis of new information that may come to our attention. The reference listed drug product upon which you based your application is subject to a period of patent protection and, therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355 (j)(4)(B)(ii), until the period has expired, i.e., April 22, 1997.

Please provide the Agency, at least 30 days prior to April 22, 1997, an amendment to this application. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved and should include updated information such as labeling, chemistry, manufacturing, and controls data as appropriate. This submission should be designated as a MINOR AMENDMENT in your cover letter. In addition to, or instead of, the amendment requested above, the Agency may, at any time prior to the final date of approval, request that you submit an amendment containing the information described above.

Failure to submit such an amendment requested by the Agency will prompt a review of the application which may result in rescission of this tentative approval letter.

Any significant change in the conditions outlined in this abbreviated application requires Agency approval before the change may be made effective.

Prior to the issuance of a final approval letter by the Agency your products are not to be deemed approved for marketing under 21 U.S.C. 355 and will not to be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list, published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to April 22, 1997, you should amend your application accordingly.

At the time you submit any amendments, you should contact Mr. Timothy W. Ames, Project Manager, at (301) 594-0309, for further instructions.

The introduction or delivery for introduction into interstate commerce of the drug before the effective approval date is prohibited under 21 U.S.C. 311(d).

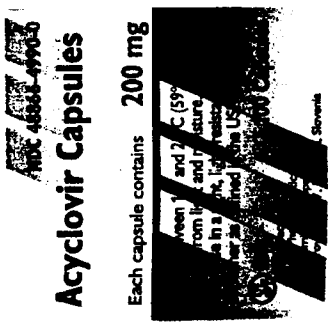
Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074750

FINAL PRINTED LABELING



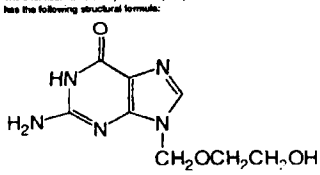
ACYCLOVIR TABLETS
ACYCLOVIR CAPSULES

DESCRIPTION: Acyclovir capsules and tablets are formulations of an antiviral drug for oral administration. Each capsule of Acyclovir contains 200 mg of acyclovir and the inactive ingredients colloidal silicon dioxide, lactose monohydrate, magnesium stearate, pregelatinized starch, sodium lauryl sulfate, and talc. The capsule shell consists of gelatin, titanium dioxide and water. Printed with edible black ink contains black iron oxide.

Each 800 mg tablet of Acyclovir contains 800 mg of acyclovir and the inactive ingredients colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Each 400 mg tablet of Acyclovir contains 400 mg of acyclovir and the inactive ingredients colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

The chemical name of acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine; it has the following structural formula:



The molecular formula of acyclovir is $C_8H_{11}N_5O_3$. Acyclovir is a white to off-white crystalline powder with a molecular weight of 225.21 and a maximum solubility in water of 2.5 mg/mL at 37°C.

CLINICAL PHARMACOLOGY: Mechanism of Antiviral Effects: Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV, and EBV[2] converts acyclovir *into* acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[3] Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase, but to a lesser degree. *In vitro*, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[5,6] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus infected cells. Thus, acyclovir is much less toxic *in vitro* for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established, but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus-infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir *in vitro*.

Microbiology: The quantitative relationship between the *in vitro* susceptibility of herpes simplex and varicella-zoster viruses to acyclovir and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 mcg/mL (plaque reduction in Vero cells) to 5.9 to 13.5 mcg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 mcg/mL to 9.9 mcg/mL (plaque reduction in Vero and GMK cells, respectively).[1]

Using a dye-uptake method in Vero cells,[9] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 HSV isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤0.9 mcg/mL acyclovir and 50% of all isolates were sensitive to ≤0.2 mcg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤2.2 mcg/mL and 50% of all isolates were sensitive to ≤0.7 mcg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.

Most of the less sensitive HSV clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TK[20] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 mcg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17 to 1.53 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.90 mcg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.6 mcg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 mcg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics: The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one uncontrolled study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection, acyclovir capsules were administered in doses of 200 to 1000 mg every 4 hours, 5 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200 mg dose were 0.49 mcg/mL (0.47 to 0.54 mcg/mL) and 0.31 mcg/mL (0.18 to 0.41 mcg/mL), respectively, and following the final 800 mg dose were 2.8 mcg/mL (2.3 to 3.1 mcg/mL) and 1.8 mcg/mL (1.3 to 2.5 mcg/mL), respectively. In another uncontrolled study of 29 younger immunocompetent patients with recurrent genital herpes simplex infections, acyclovir capsules were administered in doses of 800 mg

Pharmacokinetics: The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one uncontrolled study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection, acyclovir capsules were administered in doses of 200 to 1000 mg every 4 hours, 5 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200 mg dose were 0.49 mcg/mL (0.47 to 0.54 mcg/mL) and 0.31 mcg/mL (0.18 to 0.41 mcg/mL), respectively, and following the final 800 mg dose were 2.8 mcg/mL (2.5 to 3.1 mcg/mL) and 1.8 mcg/mL (1.3 to 2.5 mcg/mL), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes simplex infections, acyclovir capsules were administered in doses of 800 mg every 8 hours, 4 times daily for 5 days; the mean steady-state peak and trough concentrations were 1.4 mcg/mL (0.66 to 1.8 mcg/mL) and 0.55 mcg/mL (0.14 to 1.1 mcg/mL), respectively.

In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean half-life after oral doses of 360 mg/m^2 and 640 mg/m^2, in children ages 7 months to 7 years, was 2.5 hours (range 1.58 to 3.74 hours).

In a different single-dose bioavailability/bioequivalence study in 24 volunteers, one acyclovir 800 mg tablet was demonstrated to be bioequivalent to four acyclovir 200 mg capsules.

In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet and one 800 mg tablet 5 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20%, 15%, and 10%, respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir were 0.83 and 0.46 mcg/mL, 1.21 and 0.63 mcg/mL, and 1.61 and 0.83 mcg/mL for the 200, 400 and 800 mg dosage regimens, respectively.

In another study, the influence of food on the absorption of acyclovir was not apparent.

Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (8.6% to 19.6%) of the orally administered dose. The only urinary metabolite (identified by high performance liquid chromatography) is 9-[(carboxymethoxy)methyl]guanine. The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

Orally administered acyclovir in children less than 2 years of age has not yet been fully studied.

INDICATIONS AND USAGE: Acyclovir capsules and tablets are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

Acyclovir capsules and tablets are indicated for the acute treatment of herpes zoster (shingles) and chickenpox (varicella).

Genital Herpes Infections:
The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional, and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus, orally administered acyclovir is not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

First Episodes (primary and nonprimary infections-commonly known as initial genital herpes):

Double-blind, placebo-controlled studies[23,24,25] have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention, or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous acyclovir.

Recurrent Episodes: Double-blind, placebo-controlled studies[16,26-32] in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered acyclovir given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of 283 patients who received 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively. Serial analyses of the 3-month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy. Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, orally administered acyclovir should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual re-evaluation.

Limited studies[31,32] have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

Herpes Zoster Infections:
In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to acyclovir and 94 to placebo), acyclovir (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.[33]

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to acyclovir and 43 to placebo), acyclovir (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).[34]

Chickenpox:
In a double-blind, placebo-controlled efficacy study in 110 normal patients, ages 5 to 16 years, who presented within 24 hours of the onset of a typical chickenpox rash, acyclovir was administered orally 4 times daily for 5 to 7 days at doses of 10, 15, or 20 mg/kg depending on the age group. Treatment with acyclovir reduced the maximum number of lesions (336 vs. greater than 500; lesions beyond 500 were not counted). Treatment with acyclovir also shortened the mean time to 50% healing [illegible] reduced the number of vesicular lesions by the

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Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh concern or potential adverse effects. In general, orally administered acyclovir should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual re-evaluation.

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In two concurrent double-blind, placebo-controlled studies, a total of 883 normal patients, ages 2 to 18 years, were enrolled within 24 hours of the onset of a typical chickenpox rash, and acyclovir was administered at 20 mg/kg orally up to 800 mg 4 times daily for 5 days. In the larger study of 815 children ages 2 to 12 years, treatment with acyclovir reduced the median maximum number of lesions (277 vs. 380), reduced the median number of vesicular lesions by the second day of treatment (26 vs. 40), and reduced the proportion of patients with moderate to severe itching by the third day of treatment (15% vs. 34%).[36] In addition, in both studies (993 patients, ages 2 to 18 years), treatment with acyclovir also decreased the proportion of patients with fever (temperature greater than 100°F), anorexia, and lethargy by the second day of treatment, and decreased the mean number of residual lesions on Day 28.[36,37] There were no substantial differences in VZV-specific humoral or cellular immune responses measured at one month following treatment in patients receiving acyclovir compared to patients receiving placebo.[38]

Diagnosis:
Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. For patients with initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. While cutaneous lesions associated with herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may provide additional support to the clinical diagnosis.[39]

Multinucleated giant cells in smears do not distinguish varicella-zoster from herpes simplex infections.

CONTRAINDICATIONS: Acyclovir is contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations.

WARNINGS: Acyclovir capsules and tablets are intended for oral ingestion only.

PRECAUTIONS: General: Acyclovir has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in humans must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY-Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Caution should be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

Information for Patients: Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir, or they have any other questions.

Genital Herpes Infections: Genital herpes is a sexually transmitted disease and patients should avoid intercourse when visible lesions are present because of the risk of infecting intimate partners. Acyclovir capsules and tablets are for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. Acyclovir does not eliminate latent viruses. Patients are instructed to consult with their physician if they do not receive sufficient relief in the frequency and severity of their genital herpes recurrences.

There are still unanswered questions concerning reproductive/gonadal toxicity and mutagenesis; long-term studies are continuing. Decreased sperm production has been seen at high doses in some animals; a placebo-controlled clinical study using 400 mg or 1000 mg of acyclovir per day for six months in humans did not show similar findings.[40] Chromosomal breaks were seen *in vitro* after brief exposure to high concentrations. Some other currently marketed medications also cause chromosomal breaks, and the significance of this finding is unknown. A placebo-controlled clinical study using 800 mg of acyclovir per day for one year in humans did not show any abnormalities in structure or number of chromosomes.[28]

Herpes Zoster Infections: Adults age 50 or older tend to have more severe shingles, and treatment with acyclovir showed more significant benefit for older patients. Treatment was begun within 72 hours of rash onset in these studies, and was more useful if started within the first 48 hours.

Chickenpox: Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no

treatment, and decreased the mean number of lesions from Day 2 to Day 28.[36,37] There were no substantial differences in VZV-specific humoral or cellular immune responses measured at one month following treatment in patients receiving acyclovir compared to patients receiving placebo.[38]

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Multinucleated giant cells in smears do not distinguish varicella-zoster from herpes simplex infections.

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Information for Patients: Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir, or they have any other questions.

Genital Herpes Infections: Genital herpes is a sexually transmitted disease and patients should avoid intercourse when visible lesions are present because of the risk of infecting intimate partners. Acyclovir capsules and tablets are for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. Acyclovir does not eliminate latent viruses. Patients are instructed to consult with their physician if they do not receive sufficient relief in the frequency and severity of their genital herpes recurrences.

There are still unanswered questions concerning reproductive/gonadal toxicity and mutagenesis; long-term studies are continuing. Decreased sperm production has been seen at high doses in some animals; a placebo-controlled clinical study using 400 mg or 1000 mg of acyclovir per day for six months in humans did not show similar findings.[40] Chromosomal breaks were seen *in vitro* after brief exposure to high concentrations. Some other currently marketed medications also cause chromosomal breaks, and the significance of this finding is unknown. A placebo-controlled clinical study using 800 mg of acyclovir per day for one year in humans did not show any abnormalities in structure or number of chromosomes.[28]

Herpes Zoster Infections: Adults age 50 or older tend to have more severe shingles, and treatment with acyclovir showed more significant benefit for older patients. Treatment was begun within 72 hours of rash onset in these studies, and was more useful if started within the first 48 hours.

Chickenpox: Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no evidence to indicate that acyclovir treatment of chickenpox would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life. Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[41] The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 5 times a day (dosing appropriate for treatment of herpes zoster) or

200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (31 to 69 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (49 to 60 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 126 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro*. In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in humans. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day, s.c.), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day s.c. (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the one-month study and were 24 to 48 times human levels in the six-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 84 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for one month (21 to 41 times human levels) and in dogs given 80 mg/kg/day orally for one year (6 to 12 times human levels).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 105, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity,[42] in this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels.[43,44] These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when acyclovir is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS

Herpes Simplex: ***Short-Term Administration:*** The most frequent adverse events reported during clinical trials of treatment of genital herpes with orally administered acyclovir were nausea and/or vomiting in 8 of 296 patient treatments (2.7%) and headache in 2 of 296 (0.6%). Nausea and/or vomiting occurred in 2 of 267 (0.7%) patients who received placebo.

Less frequent adverse events, each of which occurred in 1 of 296 patient treatments with orally administered acyclovir (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste, and sore throat.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with acyclovir were: nausea (4.8%), diarrhea (2.4%), headache (1.9%), and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%), and rash (1.5%).

The most frequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%), and paresthesia (0.8%). Adverse events reported by 329 patients during the third year include asthenia (1.2%), paresthesia (1.2%), and headache (0.9%).

Herpes Zoster: The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%), and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%), and constipation (2.4%).

Chickenpox: The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral acyclovir in 495 patients were: diarrhea (3.2%), abdominal pain (0.8%), rash (0.6%), vomiting (0.6%), and flatulence (0.4%). The 498 patients receiving placebo reported: diarrhea (2.2%), flatulence (0.8%), and insomnia (0.4%).

Observed During Clinical Practice: Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market intro-

(6.0%), and flatulence (6.4%). The 498 patients receiving placebo reported diarrhea (2.2%), flatulence (0.8%), and insomnia (0.4%).

Observed During Clinical Practice: Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis

Nervous: confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea

Hemic and Lymphatic: leukopenia, lymphadenopathy

Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

OVERDOSAGE: Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with I.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 18 days; rabbits at s.c. and I.v. doses of 50 mg/kg/day for 13 days; and dogs at I.v. doses of 100 mg/kg/day for 31 days. A 6-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION: Treatment of Initial Genital Herpes: 200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg (two 200 mg capsules, one 400 mg tablet) 2 times daily for up to 12 months, followed by re-evaluation. See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

Intermittent Therapy: 200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodromal) of recurrence.

Acute Treatment of Herpes Zoster: 800 mg (four 200 mg capsules, two 400 mg tablets, one 800 mg tablet) every 4 hours orally 5 times daily for 7 to 10 days.

Treatment of Chickenpox: *Children (2 years of age and older):* 20 mg/kg per dose orally four times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg: 800 mg four times daily for 5 days.

Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy.

Patients With Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications:

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73 m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	> 10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	> 10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	> 25	800	every 4 hours, 5x daily
	10-25	600	every 8 hours
	0-10	800	every 12 hours

Hemodialysis: For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a six-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[45,46]

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.[47,48]

HOW SUPPLIED: Acyclovir capsules (white, opaque cap and body) containing 200 mg acyclovir and printed with „ACV 200" on cap and body - Bottle of 100 (NDC 46866-4980-0), and of 1000 (NDC 46866-4980-7).

Acyclovir tablets (white to off-white, unscored, bar-shaped) containing 800 mg acyclovir and engraved with „ACV 800" - Bottle of 100 (NDC 46866-4982-1), and of 1000 (NDC 46866-4980-5).

Acyclovir tablets (white to off-white, unscored, oval) containing 400 mg acyclovir and engraved with „ACV 400" - Bottle of 100 (NDC 46866-4986-5) and of 1000 (NDC 46866-4980-8).

Store between 15° and 25°C (59° and 77°F). Protect from light and moisture. Dispense in a tight, light-resistant container as defined in the USP. CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES:

1. O'Brien JJ, Campoli-Richards DM. Acyclovir - an updated review of its antiviral activity, pharmacokinetic properties, and therapeutic efficacy. *Drugs.* 1989;37:233-309.
2. Littler E, Zauthen J, McBride AA, et al. Identification of an Epstein-Barr virus-coded thymidine kinase. *EMBO J.* 1986;5:1959-1966.
3. Miller WH, Miller RL. Phosphorylation of acyclovir (acycloguanosine) monophosphate by GMP kinase. *J Biol Chem.* 1980; 255:7204-7207.
4. Furman PA, St Clair MH, Fyfe JA, et al. Inhibition of herpes simplex virus-induced DNA polymerase activity and viral DNA replication by 9-(2-hydroxyethoxymethyl)guanine and its triphosphate. *J Virol.* 1979; 32:72-77.
5. Derse D, Cheng YC, Furman PA, et al. Inhibition of purified human and herpes simplex virus-induced DNA polymerases by 9-(2-hydroxyethoxymethyl)guanine triphosphate: effects on primer-template function. *J Biol Chem.* 1981;256:11447-11451.
6. McGuirt PV, Shaw JE, Elion GB, et al. Identification of small DNA fragments synthesized in herpes simplex virus-infected cells in the presence of acyclovir. *Antimicrob Agents Chemother.* 1984; 25: 507-509.
7. Barry DW, Blum MR. Antiviral drugs: acyclovir. In: Turner P, Shand DG, eds. *Recent Advances in Clinical Pharmacology*, ed 3. New York: Churchill Livingstone; 1983; chap 4.
8. DeClercq E. Comparative efficacy of antiherpes drugs in different cell lines. *Antimicrob Agents Chemother.* 1982;21:661-663.
9. McLaren C, Ellis MN, Hunter GA. A colorimetric assay for the measurement of the sensitivity of herpes simplex viruses to antiviral agents. *Antiviral Res.* 1983;3:223-234.
10. Barry DW, Nesinoff-Lehrman S. Viral resistance in clinical practice:summary of five years experience with acyclovir. In: Kano R, Nakajima A, eds. Herpes Viruses and Virus Chemotherapy (Ex Med Int Congr Ser 667). New York: *Excerpta Medica*; 1985:269-270.
11. Dekker C, Ellis MN, McLaren C, et al. Virus resistance in clinical practice. *J Antimicrob Chemother.* 1983;12(suppl B):137-152.
12. Sibrack CD, Guzman LT, Willert CM, *et al.* Pathogenicity of acyclovir-resistant herpes simplex virus type 1 from an immunodeficient child. *J Infect Dis.* 1982; 146:872-882.
13. Crumpacker CS, Schnipper LE, Marlowe SI, et al. Resistance to antiviral drugs of herpes simplex virus isolated from a patient treated with acyclovir. *N Engl J Med.* 1982;306:343-346.
14. Wade JC, Newton B, McLaren C, et al. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation: a double-blind trial. *Ann Intern Med.* 1982;96:265-269.
15. Burns WH, Saral R, Santos GW, et al. Isolation and characteriza-

13. Crumpacker CS, Schnipper LE, Marlowe SI, et al. Resistance to antiviral drugs of herpes simplex virus isolated from a patient treated with acyclovir. *N Engl J Med.* 1982;306:343-346.
14. Wade JC, Newton B, McLaren C, et al. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation: a double-blind trial. *Ann Intern Med.* 1982;96:265-269.
15. Burns WH, Saral R, Santos GW, et al. Isolation and characterization of resistant herpes simplex virus after acyclovir therapy. *Lancet.* 1982;1:421-423.
16. Straus SE, Takiff HE, Seidlin M, et al. Suppression of frequently recurring genital herpes: a placebo-controlled double-blind trial of oral acyclovir. *N Engl J Med.* 1984;310:1545-1550.
17. Collins P. Viral sensitivity following the introduction of acyclovir. *Am J Med.* 1988;85:129-134.
18. Erlich KS, Mills J, Chatis P, et al. Acyclovir-resistant herpes simplex virus infections in patients with the acquired immunodeficiency syndrome. *N Engl J Med.* 1989;320:293-296.
19. Hill EL, Ellis MN, Barry DW. In: 28th Interscl Conf on Antimicrob Agents Chemother. Los Angeles: 1988, Abst. No. 0840:280.
20. Ellis MN, Keller PM, Fyfe JA, et al. Clinical isolates of herpes simplex virus type 2 that reduces thymidine kinase with altered substrate specificity. *Antimicrob Agents Chemother.* 1987;31:1117-1125.
21. Collins P, Lander BA, Oliver NM, et al. Characterization of a DNA polymerase mutant of herpes simplex virus from a severely immunocompromised patient receiving acyclovir. *J Gen Virol.* 1988;70: 875-382.
22. Field HJ, Darby G, Wildy P. Isolation and characterization of acyclovir-resistant mutants of herpes simplex virus. *J Gen Virol.* 1980; 49:115-124.
23. Bryson Y.J, Dillon M, Lovett M, et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir: a randomized double-blind controlled trial in normal subjects. *N Engl J Med.* 1983;308:916-921.
24. Mertz GJ, Critchlow CW, Benedetti J, et al. Double-blind placebo-controlled trial of oral acyclovir in first-episode genital herpes simplex virus infection. *JAMA.* 1984;252:1147-1151.
25. Nilsen AE, Aasen T, Halsos AM, et al. Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. *Lancet.* 1982;2: 571-573.
26. Douglas JM, Critchlow C, Benedetti J, et al. A double-blind study of oral acyclovir for suppression of recurrences of genital herpes simplex virus infection. *N Engl J Med.* 1984;310:1551-1556.
27. Mindel A, Weller IV, Faherty A, et al. Prophylactic oral acyclovir in recurrent genital herpes. *Lancet.* 1984;2:57-59.
28. Mattison HR, Reichman RC, Benedetti J, et al. Double-blind, placebo-controlled trial comparing long-term suppressive with short-term oral acyclovir therapy for management of recurrent genital herpes. *Am J Med.* 1986;85(suppl 2A):20-25.
29. Straus SE, Croen KD, Sawyer MH, et al. Acyclovir suppression of frequently recurring genital herpes. *JAMA.* 1988;260:2227-2230.
30. Mertz GJ, Eron L, Kaufman R, et al. The Acyclovir Study Group. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med.* 1988;85(suppl 2A): 14-19.
31. Goldberg LH, Kaufman R, Conant MA, et al. Episodic twice daily treatment for recurrent genital herpes. *Am J Med.* 1988;85:10 -13.
32. Reichman RC, Badger GJ, Mertz GJ, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir: a controlled trial. *JAMA.* 1984;251:2103-2107.
33. Hull JC, Bean B, Balfour HH Jr, et al. Therapy of herpes zoster with oral acyclovir. *Am J Med.* 1988;85(suppl 2A):85-89.
34. Morten P, Thompsen AN. Oral acyclovir in the treatment of herpes zoster in general practice. *NZ Med J.* 1989; 102:93-95.
35. Balfour HH Jr, Kelly JM, Suarez CS, et al. Acyclovir treatment of varicella in otherwise healthy children. *J Pediatr.* 1990, 116:633-639.
36. Dunkle LM, Arvin AM, Whitley RJ, et al. A controlled trial of acyclovir for chickenpox in normal children. *N Engl J Med.* 1991; 325: 1539-1544.
37. Balfour HH Jr, Rotbart HA, Feldman S, et al. Acyclovir treatment of varicella in otherwise healthy adolescents. *J Pediatr.* 1992, 120: 627-633.
38. Rotbart HA, Levin MJ, Hayward AR. Immune responses to varicella zoster virus infections in healthy children. *J Infect Dis.* 1993; 167: 195 -199.
39. Naib ZM, Nahmias AJ, Josey WE, et al. Relation of cytohistopathology of genital herpesvirus infection to cervical anaplasia. *Cancer Res.* 1973;33:1452-1463.
40. Douglas JM, David LG, Remington ML, et al. A double-blind, placebo-controlled trial of the effect of chronically administered oral acyclovir on sperm production in men with frequently recurrent genital herpes. *J Infect Dis.* 1988;157:585-593.
41. Laskin OL, deMiranda P, King DH, et al. Effects of probenecid on the pharmacokinetics and elimination of acyclovir in humans. *Antimicrob Agents Chemother.* 1982;21:804-807.
42. Stahlmann R, Klug S, Lewandowski C, et al. Teratogenicity of acyclovir in rats. *Infection.* 1987;15:261-262.
43. Lau RJ, Emery MG, Galinsky RE, et al. Unexpected accumulation of acyclovir in breast milk with estimate of infant exposure. *Obstet Gynecol.* 1987;69:468-471.
44. Meyer LJ, deMiranda P, Shaih N, et al. Acyclovir in human breast milk. *Am J Obstet Gynecol.* 1988; 158:586-588.
45. Laskin OL, Longstreth JA, Whelton A, et al. Effect of renal failure on the pharmacokinetics of acyclovir. *Am J Med.* 1982;73:197-201.
46. Keamy HC, Lieo SH, deMiranda P, et al. Influence of hemodialysis on acyclovir pharmacokinetics in patients with chronic renal failure. *Am J Med.* 1982;73:202-204.
47. Beelaert J, Schurgers M, Dancais R, et al. Multiple dose pharmacokinetics of intravenous acyclovir in patients on continuous ambulatory peritoneal dialysis. *J Antimicrob Chemother.* 1987;20:69-76.
48. Shah GM, Winer RL, Keamy HC. Acyclovir pharmacokinetics in a patient on continuous ambulatory peritoneal dialysis. *Am J Kidney Dis.* 1988;7:507-510.

Lek
Pharmaceutical and Chemical Company d.d.
Ljubljana, Slovenia
Printed in Slovenia

February 1997

481904

OPEN HERE

NDC 48866-4990-7

Acyclovir Capsules

Each capsule contains 200 mg

Store between 15° and 25°C (59° and 77°F).
Protect from light and moisture.
Dispense in a tight, light-resistant container as defined in the USP.

1000 Capsules

lek

Manufactured by
Lek Pharmaceutical and
Chemical Company d.d.
Verovškova 57 Ljubljana Slovenia

7 | 0 6 4 1 2 4 9 9 0 7 | 3

Made in Slovenia

CAUTION: Federal law prohibits dispensing without prescription.

For indications, dosage, precautions, etc., see accompanying package insert.

Exp. date:

Lot & Mnf. date:

481912

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074750

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VI
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-750

3. NAME AND ADDRESS OF APPLICANT
Lek Pharmaceutical and Chemical Company d.d.
Verovškova 57
61107 Ljubljana
Slovenia

4. LEGAL BASIS FOR SUBMISSION
ZOVIRAX® Capsules, 200 mg
Glaxo Wellcome
3030 Cornwallis Road
Research Triangle Park, NC 27709

Acyclovir is covered by Patent #4199574, Expiration Date April 22, 1997. The firm acknowledged the patent. An exclusivity for the treatment of varicella infections expired February 26, 1995.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:

9/15/95	Original submission.
4/22/96	Amendment - Response to Agency's Bioequivalence Request for Information letter of 3/18/96.
8/7/96	Amendment - Response to Agency's letter of 5/21/96.
9/23/96	Correspondence - Inclusion of Bioequivalence Dissolution Specifications.
2/17/97	**Amendment - Response to Agency's Facsimile Request of 2/4/97.**

FDA:

10/23/95	Receipt acknowledged.
3/18/96	Issuance of Bioequivalence Request for Information letter.
5/21/96	Issuance of Not Approvable letter.
9/6/96	Issuance of Bioequivalence No Further Questions letter.
2/4/97	Issuance of Facsimile Minor Amendment.

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4-Confid Comm

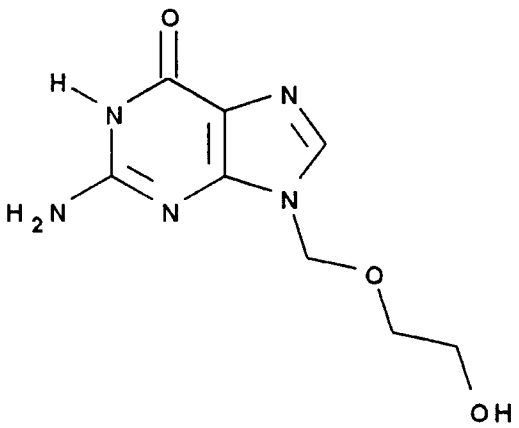
(b)4-Confid Comm

13. DOSAGE FORM
Hard Gelatin Capsule
for oral administration

14. POTENCIES
200 mg/capsule

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP
$C_8H_{11}N_5O_3$; M.W. = 225.21
CAS [59277-89-3]



1. 9-[(2-Hydroxyethoxy)methyl]guanine.

2. 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)-methyl]-

USP: White to off-white crystalline powder. Melts at temperatures higher than 250°, with decomposition. Soluble in 0.1 N hydrochloric acid; sparingly soluble in water; insoluble in alcohol.

Merck: Crystals from methanol, mp 256.5° - 257°. LD_{50} in mice (mg/kg): > 10,000 orally; 1000 i.p.

16. RECORDS AND REPORTS
3/8/96 - Bioequivalence review, M. Park.
3/20/96 - Labeling review, C. Hoppes.
3/13/96 - Chemistry review #1, G.J. Smith.
8/27/96 - Bioequivalence review, M. Park.
9/3/96 - Labeling review, J. White.
1/21/97 - Chemistry review #2, G.J. Smith.
2/26/97 - Labeling review, J. White.

17. COMMENTS
The firm has resolved all major questions regarding the chemistry, manufacturing and controls sections of the application.

Labeling was found to be satisfactory.

The Division of Bioequivalence found the drug product equivalent to the listed drug.

An acceptable EIR was issued by the Office of Compliance.

Methods Validation was found satisfactory.

DMF for drug substance was satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
The application may be granted Tentative Approval.

19. REVIEWER: DATE COMPLETED:
Glen Jon Smith March 4, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074750

BIOEQUIVALENCE REVIEW(S)

MAR 8 1996

D,V

Acyclovir Capsules	LEK
200 mg Capsules	Ljubljana, Slovenia
ANDA #74-750	Submission Date:
Reviewer: Moo Park	September 15, 1995
Filename: 74750SD.995	February 16, 1996

Review of Two BE Studies and Dissolution Data

I. Objectives

Review of Lek's two *in vivo* bioequivalence studies comparing its 200 mg strength Acyclovir Capsules to Burroughs Wellcome's 200 mg strength Zovirax Capsules under fasting and non-fasting conditions. The firm submitted *in vitro* dissolution data for review.

II. Background

Acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine, a synthetic purine nucleoside analog with in vivo and in vitro inhibitory activity against (in decreasing order) herpes simplex types 1 and 2 viruses, varicella zoster virus, Epstein-Barr virus, and cytomegalovirus. Acyclovir is converted by enzymes present in virus-infected cells into an active form, acyclovir triphosphate, which interrupts viral DNA replication. Acyclovir capsules and suspension are indicated for treatment of initial episodes and management of recurrent herpes simplex virus genitalis in certain patients. The capsule, suspension, and tablet dosage forms are indicated for treatment of acute herpes zoster and chicken pox.

Acyclovir oral absorption is slow, variable, and incomplete, with absolute bioavailability estimated at about 15-30%. Peak blood concentrations occur approximately 1.5-2.5 hours following oral dosing. There are no active metabolites. Studies in which 0.5 to 15 mg/kg were administered IV to patients with normal renal function yielded elimination half-lives of 2 to 3 hours. Renal excretion is the major route of elimination with 45-79% of a dose recovered unchanged in the urine.

Acyclovir is marketed as Zovirax Burroughs-Wellcome) 200 mg capsules (NDA #18-828, 1/25/85), 800 mg and 400 mg tablets (NDA #20-089, 4/30/91), and oral suspension 200 mg/5 ml (NDA #19-909, 12/22/89).

III. Summary of Bioequivalence Study Procedures

A. BE Study under Fasting Conditions

1. Protocol # N/A

2. Study # 9504ACI-1

3. Brief description of the study

This randomized, single-dose, two-way crossover study was conducted with 27 healthy male volunteers in accordance with the Protocol. In each period, subjects received a single 200 mg dose of either LEK's Acyclovir Capsules or BW's Zovirax Capsules following an overnight fast. There was a one-week washout between treatments. Blood samples were collected pre-dose and over 24 hours after each dose. Plasma concentration of acyclovir was measured by a fully validated HPLC procedure. Pharmacokinetic and statistical analyses were performed to compare the test and reference treatments.

4. Objective of the study:

The objective of this study was to determine the bioequivalence of two acyclovir capsule formulations after administration of single doses to healthy volunteers under fasting conditions.

5. Study design: Randomized, single-dose, two-way crossover study under fasting conditions.

6. Study sites:

Clinical study:

Analytical study:

(b)4 - Confid Comm

7. Study dates:

Clinical study: 1/14/95-1/15/95 (Period 1)
1/21/95-1/22/95 (Period 2)

Analytical study: N/A

8. Investigators:

(b)4- Confid Comm

(b)4 Confid Comm

9. Drug Products:

A. Test: 200 mg Acyclovir Capsules (LEK, Lot #2411094)

B. Reference: 200 mg Zovirax® Capsules (Burroughs Wellcome, Lot #401622)

10. Dosing: All doses were administered with 240 ml of room temperature water following an overnight fast.

11. Subjects: Twenty-seven (27) subjects who entered in this study were normal healthy male volunteers in the age range of 20-45 years, and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the absence of any clinically significant findings on the medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

12. Confinement: During the confinement periods of this study, the subjects were housed and fed at the clinical facility. [redacted]

13. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 240 mL of tap water. 200 mL of soft drink containing no xanthine was provided at 2 hours post-dose. Water was allowed ad lib. after 4 hours post-dose.

14. Washout period: One week.

15. Blood samples: In each period, 10 mL of blood samples were collected at 0, 0.33, 0.66, 1, 1.33, 1.66, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours. Plasma was separated and all plasma samples were stored frozen at -18°C until transfer to the laboratory for analysis.

16. Subject safety monitoring: Subjects were asked to spontaneously report any signs or symptoms that might be related to the drug products.

17. Adverse reactions: On each dosing period subjects were asked to report any signs or symptoms judged to be drug related.

18. Analytical procedure: Plasma samples were packaged in a freezer and shipped to the analytical laboratory. The plasma samples were assayed by a HPLC method with UV detector.

19. Pharmacokinetic and statistical analysis: Statistical analyses were performed on the pharmacokinetic parameters for acyclovir. 90% confidence intervals were calculated for AUCT,

AUCI and CMAX.

B. BE Study under Non-fasting Conditions

1. Protocol # N/A

2. Study # 9505 ACI2

3. Study design: Randomized, single-dose, three-way crossover study under fasting/non-fasting conditions.

4. Study sites:

Clinical study:

Analytical study:

(b)4-Confid Comm

5. Study dates:

Clinical study: 2/4/95-2/5/95 (Period 1)
2/11/95-2/12/95 (Period 2)
2/18/95-2/19/95 (Period 3)

Analytical study: 4/19/95-5/11/95

6. Investigators:

(b)4-Confid Comm

7. Treatments/Drug Products:

A. Test: 200 mg Acyclovir Capsules (LEK, Lot #2411094) under non-fasting conditions.

B. Reference: 200 mg Zovirax® Capsules (Burroughs Wellcome, Lot #401622) under non-fasting conditions.

C. Test: 200 mg Acyclovir Capsules (LEK, Lot #2411094) under fasting conditions.

8. Dosing: All doses were administered with 240 ml of room temperature water following an overnight fast or within 10 minutes after consuming the breakfast depending on the dosing schedule.

9. Subjects: Sixteen (16) subjects who were entered in this study were normal healthy male volunteers in the age range of 20-40 years, and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the absence of any clinically significant findings on the medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

10. Confinement: During the confinement periods of this study, the subjects were housed and fed at the clinical facility.

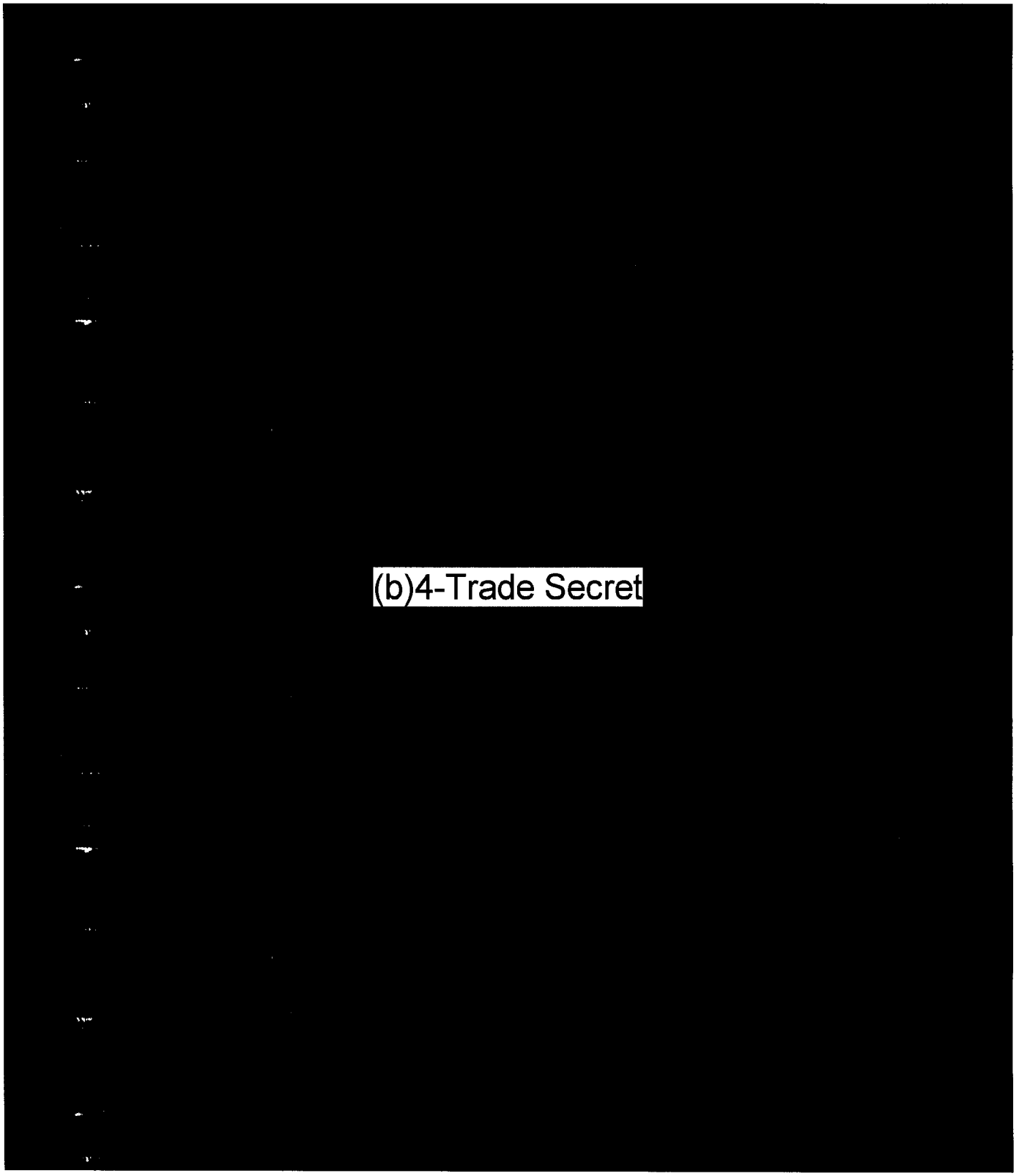
11. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 240 mL of tap water. 200 mL of soft drink containing no xanthine was provided at 2 hours post-dose. Water was allowed ad lib. after 4 hours post-dose.

12. Washout period: One week.

13. Blood samples: In each period, 10 mL of blood samples were collected at 0, 0.33, 0.66, 1, 1.33, 1.66, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours. Plasma was separated and all samples were stored frozen at -18°C until analysis.

IV. Validation of Assay Method for Plasma Samples

(b)4-Trade Secret


(b)4-Trade Secret

(b)4-Trade Secret

V. *In Vivo* BE Study Results with Statistical Analysis

A. Study under fasting conditions

A total of 28 subjects were recruited for the study but only 27 participated in the study and completed two periods of study successfully. There was no drop-out and there was no missing sample.

Adverse reactions were followed according to the protocol of the study. No clinically significant adverse reactions were reported.

1. Mean plasma levels

The mean plasma levels for the test and reference products are comparable as shown in Table 2 and Fig. P-1. The test/reference ratios (RMEAN12) for the mean plasma levels range from 0.99 to 1.40.

Table 2. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	0.03	0.04	0.03	0.04	1.05
0.67	0.22	0.12	0.16	0.08	1.40
1	0.30	0.13	0.26	0.09	1.18
1.33	0.33	0.12	0.31	0.12	1.07
1.67	0.32	0.11	0.31	0.14	1.04
2	0.30	0.11	0.29	0.13	1.03
2.5	0.27	0.09	0.27	0.12	0.99
3	0.24	0.08	0.24	0.10	[illegible]
4	0.19	0.08	0.18	0.07	1.04
6	0.12	0.05	0.11	0.04	1.08
8	0.07	0.03	0.07	0.03	1.05
10	0.05	0.02	0.04	0.02	1.11
12	0.04	0.02	0.03	0.02	1.40
24	0.00	0.01	0.00	0.01	1.11

UNIT: PLASMA LEVEL=MCG/ML TIME=HRS
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=TEST/REF RATIO

2. Pharmacokinetic parameters

The test/reference ratios for the non-transformed and log-transformed AUCT, AUCI and CMAX range 1.0-1.10 as shown in Table 3. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the 80-125% range as shown in Table 4.

Table 3. EST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1.94	0.59	1.79	0.62	1.08
AUCT	1.71	0.56	1.58	0.55	1.08
CMAX	0.38	0.12	0.35	0.14	1.08
KE	0.22	0.07	0.22	0.08	1.00
LAUCI*	1.84	0.34	1.70	0.32	1.08
LAUCT*	1.61	0.36	1.49	0.34	1.08
LCMAX*	0.36	0.35	0.33	0.38	1.10
THALF	4.50	4.25	4.14	3.06	1.09
TMAX	1.35	0.51	1.57	0.62	[redacted]

UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR

Table 4. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	1.94	1.80	[redacted]	[redacted]
AUCT	1.71	1.58		
CMAX	0.38	0.35		
LAUCI	1.84	1.71		
LAUCT	1.61	1.50		
LCMAX	0.36	0.33		

(b4) (b)4

UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR

B. Study under non-fasting Conditions

A total of 16 subjects participated and completed three periods of the study successfully. There was no drop-out and there was no missing sample.

Adverse reactions were followed according to the protocol of the study. No clinically significant adverse reactions were reported.

1. Mean plasma levels

Table 5 and Fig. P-2 show the plasma acyclovir-time data for the food study. The food effect was not clear-cut according to the data in Table 5: The mean peak concentrations were 0.35 mcg/mL for all three treatments. The time for the peak concentrations were 2 hours for the test and reference products under non-fasting conditions and 1.66 hours for the test product under fasting conditions. It appears that under non-fasting conditions the test product showed 15-17% higher concentrations over the reference product. See the RMEAN12 in Table 5, which is the ratio of test/reference under non-fasting conditions.

Table 5. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST-FOOD
MEAN2=REFERENCE-FOOD
MEAN3=TEST-FASTING

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	0.00	0.01	0.00	0.01	0.03	0.03
0.67	0.03	0.06	0.03	0.04	0.21	0.11
1	0.09	0.13	0.11	0.13	0.30	0.14
1.33	0.21	0.13	0.22	0.16	0.33	0.19
1.67	0.30	0.08	0.30	0.13	0.35	0.21
2	0.35	0.05	0.35	0.11	0.35	0.21
2.5	0.35	0.08	0.31	0.08	0.33	0.19
3	0.34	0.10	0.29	0.07	0.29	0.17
4	0.29	0.10	0.25	0.08	0.21	0.14
6	0.15	0.05	0.14	0.04	0.11	0.06
8	0.08	0.03	0.08	0.02	0.07	0.04
10	0.05	0.02	0.05	0.02	0.04	0.03
12	0.03	0.02	0.03	0.02	0.02	0.02
24	0.01	0.01	0.00	0.01	0.01	0.01

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.33	1.17	0.16	0.14
0.67	1.17	0.14	0.12
1	0.82	0.30	0.37
1.33	0.93	0.62	0.67
1.67	1.02	0.86	0.85
2	1.00	0.99	0.99
2.5	1.15	1.07	0.94
3	1.15	1.17	1.02
4	1.16	1.37	1.18
6	1.08	1.32	1.22
8	1.03	1.21	1.17
10	1.12	1.26	1.12
12	1.02	1.35	1.32
24	3.00	1.88	0.63

UNIT: PLASMA LEVEL=MCG/ML TIME=HRS

2. Pharmacokinetic parameters

The test/reference ratios for the PK parameters under non-fasting conditions are shown as RMEAN12 in Table 6. The ratios for the log-transformed AUCT, AUCI and CMAX are 1.14, 1.16, and 1.03, respectively. The ratios met the requirements by the Agency.

The ratios (RMEAN12, RMEAN13 and RMEAN23) show that there is no clear-cut food effect.

Table 6. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)
MEAN1=TEST-FOOD
MEAN2=REFERENCE-FOOD
MEAN3=TEST-FASTING

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	2.21	0.64	1.90	0.51	1.98	1.02
AUCT	1.95	0.50	1.70	0.41	1.78	0.95
CMAX	0.40	0.07	0.39	0.08	0.43	0.21
KE	0.22	0.13	0.24	0.09	0.22	0.10
LAUCI*	2.13	0.29	1.84	0.26	1.74	0.53
LAUCT*	1.89	0.25	1.66	0.24	1.55	0.55
LCMAX*	0.40	0.16	0.38	0.22	0.38	0.49
THALF	5.80	5.69	4.08	3.81	4.57	4.19
TMAX	2.39	0.66	2.15	0.72	1.42	0.61

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.16	1.11	0.96
AUCT	1.14	1.10	0.96
CMAX	1.03	0.94	0.92
KE	0.94	1.00	1.07
LAUCI	1.16	1.22	1.06
LAUCT	1.14	1.22	1.07
LCMAX	1.03	1.04	1.01
THALF	1.42	1.27	0.89
TMAX	1.11	1.68	1.51

VI. Formulation

Table 7. shows the composition of the test products, 200 mg Acyclovir Capsules by LEK. The reference product contains corn starch, lactose, magnesium stearate and sodium lauryl sulfate.

Table 7. Composition of LEK's Acyclovir Capsules

Ingredient	Amount, mg
Acyclovir, USP 23	200
Lactose monohydrate, NF 18	[redacted]
Pregelatinized starch, NF 18	
Talc, USP 23	(b)4
Sodium lauryl sulfate, NF 18	ts
Colloidal silicon dioxide, NF 18	
Magnesium stearate, NF 18	
Total	400

VII. In Vitro Testing

1. Potency and content uniformity [redacted]

Assay and content uniformity data are summarized for the test and reference products in Table 8. The batch size of the test product was [redacted](b)4cc[redacted]

Table 8. Potency and Content Uniformity

Product	Lot No.	Potency, %	Content uniformity (%CV)
Zovirax, 200 mg	401622	101.0	102.3 (1.7)
Test, 200 mg	2411094	100.4	100.6 (1.9)

2. Dissolution testing data

The dissolution testing was performed in 900 mL of 0.1 N HCl using apparatus 1 (paddle) at 100 rpm with dissolution specifications of NLT [redacted](b)4 dissolved in 30 minutes (see Table 9). The FDA method calls for water as dissolution medium instead of 0.1 HCl used in the dissolution testing. The firm is recommended to perform the dissolution testing in water and submit the data for review:

FDA method:

Medium: 900 mL water
Apparatus 1 (basket) at 100 rpm
Tolerances: NLT [redacted](b)4 in 30 minutes

VIII. Comments

1. Study under fasting conditions (200 mg capsules):

A total of 28 subjects were recruited but only 27 participated and completed two periods of study successfully. There was no drop-out and there was no missing sample.

The mean plasma levels for the test and reference products are comparable. The test/reference ratios (RMEAN12) for the mean plasma levels range from 0.99 to 1.40.
The test/reference ratios for the non-transformed and log-transformed AUCT, AUCI and CMAX range 1.0-1.10 as shown in Table 3. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the 80-125% range.

2. Study under non-fasting Conditions (200 mg capsules):

A total of 16 subjects participated in the study and completed three periods of the study successfully. There was no drop-out and there was no missing sample.

The food effects were inconclusive: The mean peak concentrations were 0.35 mcg/mL for all three treatments. It appears that under non-fasting conditions the test product showed 15-17% higher concentrations over the reference product. The ratios for the log-transformed AUCT, AUCI and CMAX were 1.14, 1.16, and 1.03, respectively. The ratios met the requirements by the Agency.

3. Assay validation: Pre-study validation and within-study validation are acceptable except the recovery data which were not submitted.

4. Adverse reaction (200 mg capsules): No clinically significant adverse reactions were reported for the fasting and non-fasting studies.

5. The batch size of the 200 mg test product was [redacted]

6. The formulation of the 200 mg test product does not contain inactive ingredients which may adversely affect its bioavailability.

7. The dissolution testing was done in 0.1 N HCl. The firm is requested to use 900 mL water as the dissolution medium in apparatus 1 at 100 rpm with tolerances of NLT [redacted] in 30 minutes.

IX. Deficiencies

1. The firm is requested for the comparative dissolution testing

using 900 mL water as the dissolution medium in apparatus 1 at 100 rpm. Tolerances are NLT [redacted] (Q) in 30 minutes.

2. Submit the recovery data obtained during pre-study assay validation.

X. Recommendation

The *in vivo* bioequivalence study conducted under fasting and non-fasting conditions by LEK on its Acyclovir Capsules, 200 mg strength, lot #2411094, comparing it to Burroughs Wellcome's Zovirax® Capsules, 200 mg strength, lot #401622, has been found incomplete by the Division of Bioequivalence. The applicant should be informed of the deficiencies #1-2.

The firm should be informed of the deficiencies and recommendation.

[redacted] /S/

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

[redacted] 3/8/96

Concur: [redacted] /S/ Date: 3/8/96

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-750 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-658 (Mhatre, Park), Drug File, Division File

File history: Draft(2/27/96);Final (3/7/96)

Table 9. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Acyclovir Capsules					
Strength	200 mg					
ANDA Number	74-750					
Applicant	LEK					
Reference Drug Product	Burroughs Wellcome's 200 mg strength Zovirax® Capsules					
II. USP Method for Dissolution Testing						
Medium and Volume	900 mL 0.1 N HCl					
Apparatus and rpm	Basket, 100 rpm					
Time	30 min					
Tolerances	(b)4					
Assay Method	(b)4					
III. Dissolution Data (%)						
Time	Test Product Lot No:2411094 Strength:200 No of Units:12			Reference Product Lot No:401622 Strength:200 No of Units:12		
Min	Mean	Range	%CV	Mean	Range	%CV
10	98	(b)4	1.1	88.1	(b)4	13.8
20	99.2		1.0	100.3		2.8
30	99.1		1.0	100.5		2.9

ANDA 74-750

SEP - 6 1996

LEK Pharmaceutical and Chemical Co. d.d.
Attention: Andrej Gasperlin
Authorized U.S. Agent
333 Sylvan Avenue, 2nd Floor
Englewood Cliffs NJ 07632

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Capsules 200 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than [illegible] of the labeled amount of acyclovir in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

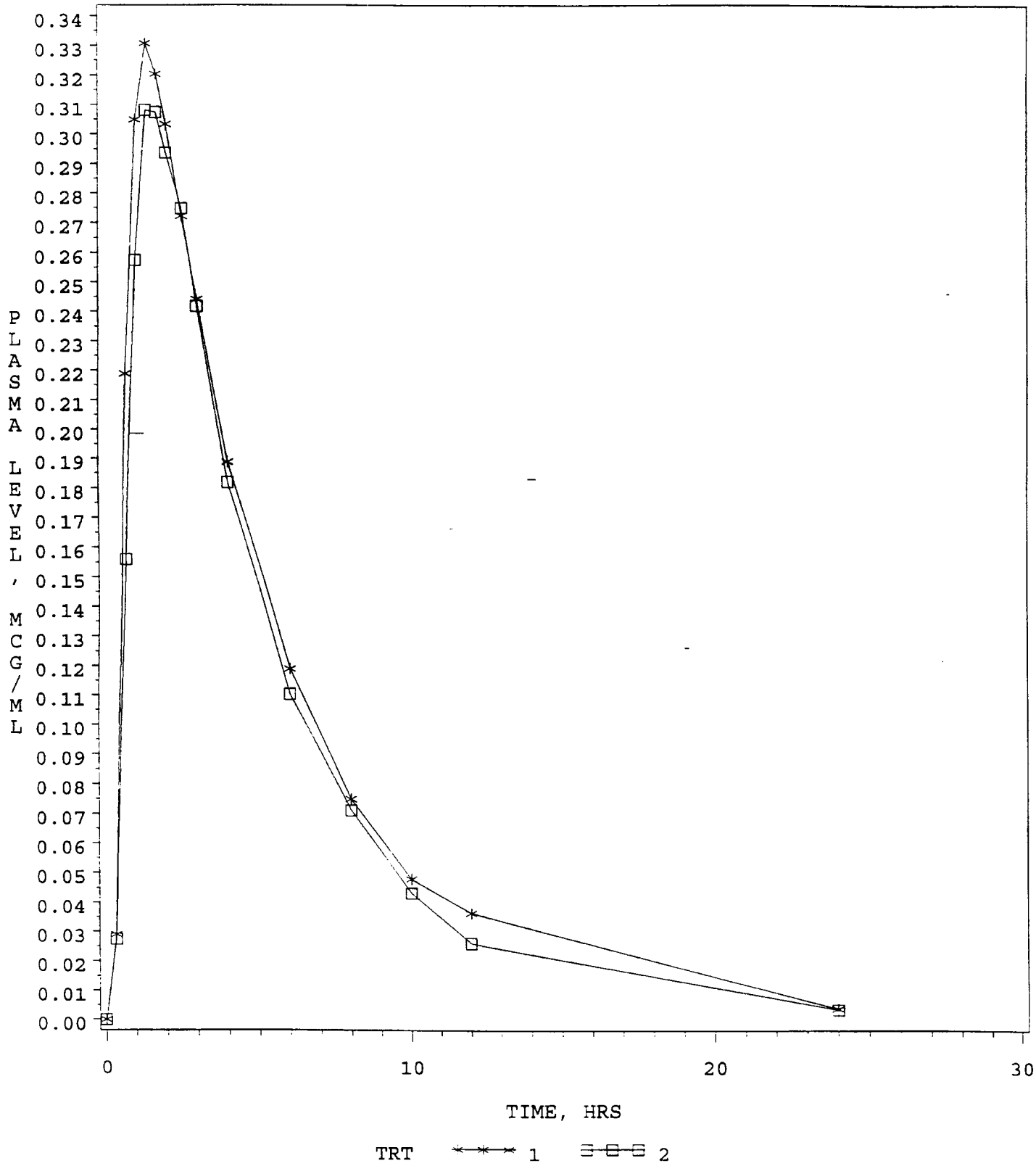
Sincerely yours,

/s/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FIG P–1. PLASMA ACYCLOVIR LEVELS

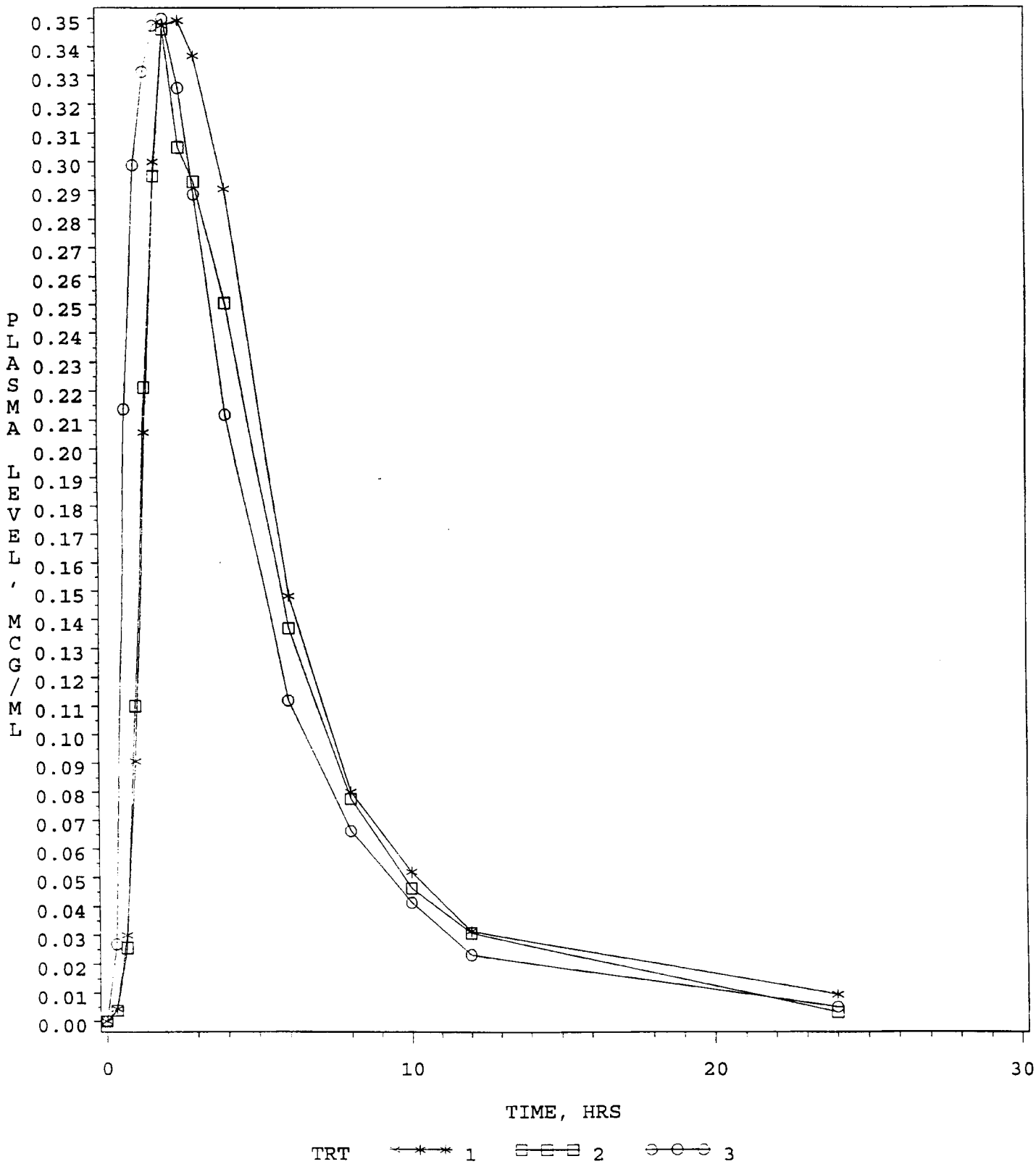
ACYCLOVIR CAPSULES, 200 MG, ANDA #74-750
UNDER FASTING CONDITIONS
DOSE=200 MG



1=TEST PRODUCT(LEK) 2=REFERENCE PRODUCT(BW)

FIG P-2. PLASMA ACYCLOVIR LEVELS

ACYCLOVIR CAPSULES, 200 MG, ANDA #74-750
UNDER NON-FASTING CONDITIONS
DOSE=200 MG



1=TEST-NONFASTING(LEK) 2=REF-NONFASTING(BW) 3=TEST-FASTING(LEK)